

MINUTES OF THE
**PEDIATRIC ETHICS SUBCOMMITTEE of the
PEDIATRIC ADVISORY COMMITTEE**

Holiday Inn Gaithersburg, 2 Montgomery Avenue, Gaithersburg, Maryland

June 9th and 10th, 2008

On June 9th, 2008 the meeting was convened at approximately 8:00 a.m. and on June 10th, 2008 the meeting was convened at approximately 8:30 a.m..

Subcommittee Members and Consultants Present for June 9th and 10th, 2008

Norman Fost, M.D., M.P.H. (*Subcommittee Chair*)
Jeffrey R. Botkin, M.D., M.P.H. (Consultant)
Amy Celento (Subcommittee Member)
Alan Fix, M.D., M.S. (Consultant)
Leonard Glantz, J.D. (Consultant)
Steven Joffe, M.D., M.P.H. (Consultant)
Alexander Kon, M.D. (Consultant)
Theresa O'Lonegan, M.A. (Consultant)
Geoffrey Rosenthal, M.D. (Subcommittee Member)
Elaine Vining (Subcommittee Member)
Benjamin Wilfond, M.D. (Consultant)

Executive Secretary

Carlos Peña, Ph.D., M.S.

FDA Participants

Therese Cvetkovich, M.D.
Virginia Elgin, M.D.
Karen Midthun, M.D.
Dianne Murphy, M.D.
Robert "Skip" Nelson, M.D., Ph.D.
Celia Witten, M.D., Ph.D.

Open Public Hearing Speakers

A public letter to the FDA from Bernard Yablin, MD, was read into the meeting transcript.
Dr. Michelle Lally, Brown University
Mr. Jeff Safrit, Elizabeth Glaser Pediatric Aids Foundation

Presentations

Meeting Agenda Overview

Robert "Skip" Nelson, M.D., Ph.D., Office of Pediatric Therapeutics (OPT), Office of the Commissioner (OC)

Presentation: 21 CFR 50, Subpart D

Robert "Skip" Nelson, M.D., Ph.D., OPT, OC

Presentation of Hypothetical Case One: Enrolling Adolescents in an HIV Vaccine Clinical Study

Robert "Skip" Nelson, M.D., Ph.D., OPT, OC

Presentation: Choice of Control Group

Robert "Skip" Nelson, M.D., Ph.D., OPT, OC

Presentation of Hypothetical Case Two: Study of ICS in Children with Mild Persistent Asthma

Robert "Skip" Nelson, M.D., Ph.D., OPT, OC

Presentation: Prospect of Direct Benefit from Animal Studies

Robert "Skip" Nelson, M.D., Ph.D., OPT, OC

Presentation of Hypothetical Case Three: Stem Cells for Neonatal Hypoxic-Ischemic Injury

Robert "Skip" Nelson, M.D., Ph.D., OPT, OC

Summary of FDA Questions and Committee Discussions

Presentation of Hypothetical Case One: Enrolling Adolescents in an HIV Vaccine Clinical Study

Committee Questions –

1. Please discuss the ethical considerations that should go into a decision about whether (and, if yes, when) to enroll adolescents in the above phase 2 clinical investigation. As part of your discussion, please address the threshold of evidence necessary to establish that the study intervention offers a sufficient prospect of direct benefit to justify the risks of vaccine administration. For example, are interim or final results from adult phase 2 or 3 studies needed prior to studies in adolescents? How does the lack of an immunological surrogate for clinically meaningful benefit affect the prospect of direct benefit?

Committee Discussion –

The Subcommittee commented upon a number of factors which might impact on whether and when to enroll adolescents in clinical investigations. Starting with the importance of scientific necessity, the Subcommittee identified such factors as age, behavioral considerations, the likelihood of physiological differences, "at risk" populations, clinical trial target populations, relative efficacy across different study populations, pre-existing safety and effectiveness data, and the risk benefit analysis as important considerations. The Subcommittee identified scientific necessity, extrapolation, prospect of direct benefit, risk of the intervention, the disorder or condition to be treated, and qualifying "direct benefit" as issues to evaluate in designing a clinical investigation. The Subcommittee agreed on the importance of studies in children when scientifically appropriate, and both patient and parental consent are important components of the enrollment process.

Presentation of Hypothetical Case Two: Study of ICS in Children with Mild Persistent Asthma

Committee Questions –

1. Please discuss the assessment of the potential benefits of this clinical investigation for the enrolled children.
2. Please discuss the assessment of the risks of this clinical investigation for the enrolled children.
3. Please discuss the analysis of this proposed trial under Subpart D. In your discussion, please address whether the different study arms should be evaluated together (i.e., as one cohort before randomization) or separately (i.e., as separate cohorts after randomization).

Committee Discussion –

The Subcommittee discussed the prospect of direct benefit for different treatment groups and commented that both the benefit to the child and risk of the intervention are important considerations for each treatment arm in a clinical investigation. The Subcommittee discussed trial design, including the risk of being in a placebo group; trial impact (e.g. enrollment, management, treatment paradigm, and increased access to healthcare); and compensation, and how these factors may influence potential benefit to the subject. The Subcommittee also commented upon equipoise, standard of care, and pre- and post-randomization analyses as additional components to consider when assessing potential benefits of a clinical investigation for an individual subject.

Presentation of Hypothetical Case Three: Stem Cells for Neonatal Hypoxic-Ischemic Injury

Committee Questions –

1. Please discuss the ethical issues in selecting an appropriate subject population for the initial clinical development plan of these HNSC products.
2. Please discuss the ethical issues in designing a “first-in-children” clinical trial of these HNSC products.

Committee Discussion –

The Subcommittee discussed the purpose of the study and targeted outcomes – e.g., the ability to measure physiologic and clinical outcomes - as important ethical considerations, when designing a study and determining the appropriate subject population. The definition and assessment of direct benefit was discussed, including the use of surrogate markers, the pros and cons of younger vs. older subjects, various regulatory approaches for the appropriate review of a pediatric clinical investigation, the use of “compassionate use” and “innovative therapy” models as justifications, limits of animal studies, and the use of adult models as proof of concept prior to pediatric studies.

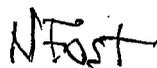
On June 9th, 2008 the meeting adjourned at approximately 5:00 p.m. and on June 10th, 2008 the meeting adjourned at approximately 12:00 p.m..

Please see transcript for details

I certify that I attended the June 9th and 10th, 2008 meeting of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.



Carlos Peña, Ph.D., M.S.
Executive Secretary



Norman Fost, M.D., M.P.H.
Chair